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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/670,004	09/25/2003	Kazuhiro Aikawa	Q77153	6236

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EXAMINER
KISHORE, GOLLAMUDI S

ART UNIT	PAPER NUMBER
1612	

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09/21/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/670,004	AIKAWA, KAZUHIRO	
	Examiner	Art Unit	
	Gollamudi S. Kishore	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 5-12-09 is acknowledged.

Claims included in the prosecution are 1 and 4-6.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1 and 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over in combination with EP 0583 665, Aikawa (7,101,532) or Kitaguchi (7,008,614) or Schmidt (6,077,529), Mjalli (7,087,632) individually or in combination.

2. Claims 1 and 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0583 665 cited above in view of Aikawa (7,101,532) or Kitaguchi (7,008,614) or Schmidt (6,077,529) individually or in combination.

EP as discussed before teaches liposomes containing PC and PS in 1:1 molar ratio. The benzimidazole however, is added to the medium containing the liposomes. According to EP the benzimidazole derivatives are for the treatment of hyperlipidemia and arteriosclerosis.

Aikawa and Kitaguchi while disclosing liposomal compositions for radiography of a vascular disease (atherosclerosis) teach that liposomes are selectively taken up by vascular smooth muscle cells and macrophages. The liposomes contain PC and PS in

1:1 molar ratio and the hydrophobic active agent is in the membrane (abstract, Examples 5, 68 and 9 of Aikawa; abstract, Examples 4, 5 and 8 of Kitaguchi).

Schmidt discloses that liposomes are useful in handling arteriosclerosis. The phospholipids, which could be used in making the liposomes, include PC and PS (abstract, col. 5, lines 24-34 and claim 4).

Mjalli discloses liposomal formulations containing benzimidazoles for the treatment of atherosclerosis (abstract, col. 2, line 56, col. 37, lines 44-50 and claims). Mjalli however, does not specifically teach liposomes containing both phosphatidylcholine and PS. Mjalli just teaches that liposomes can be made from a variety of phospholipids on col. 37, lines 44-50).

Assuming that the benzimidazole derivatives of EP are not associated with the liposomal membrane: it would have been obvious to one of ordinary skill in the art to encapsulate or associate the benzimidazole derivatives of EP in liposomes since the references of Kitaguchi, and Aikawa each teach that the liposomes are selectively taken up by vascular smooth muscle cells and macrophages and since the reference of Schmidt teaches that liposomes can be used in handling atherosclerosis. One of ordinary skill in the art would be motivated to use liposomes as delivery vehicles with a reasonable expectation of success since Mjalli who teaches the use of benzimidazole derivatives for atherosclerosis is suggestive of the use of liposomes as delivery vehicles.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues the following: "the presently claimed liposome in which the

membrane components of (i), (ii), and (iii) are added at the same time, provides a crucial distinguishing feature over the cited art because this feature allows for the incorporation of benzimidazole into the membrane of the claimed liposome. This is consistent with M.P.E.P. § 2113, in which the "structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where theproduct can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. Furthermore, this feature is responsible for the unexpectedly enhanced uptake of benzimidazole compounds by macrophages as evidenced by the data shown in the Rule 132 Declaration submitted January 17, 2008, which would not have been predictible based upon the disclosures of the cited art. Thus, for at least the following reasons and those previously argued, the presently claimed invention is neither taught nor suggested by EP '665, Aikawa I, Kitaguchi, Schmidt, or Mjalli, either alone or in combination. Applicants note the Office Action has failed to establish a prima-facie case of obviousness because the prior art references do not teach or suggest all the claim limitations. M.P.E.P. § 2143. First, EP '665 discloses the separate addition of benzimidazole compound to an already formed liposome mixture (see page 33 of EP '665). EP '665 does not teach or suggest incorporation of a benzimidazole compound into liposomes to prepare the presently claimed liposomes wherein the benzimidazole is combined with the lipid components in a mixture at the same time. Second, Aikawa I and Kitaguchi do not cure this deficiency because Aikawa I and Kitaguchi are each relied upon for merely disclosing a process of adding a compound as an active ingredient after liposomes have formed. Schmidt is even less relevant because Schmidt is merely relied upon for disclosing liposomes to handle arteriosclerosis and extract cholesterol. The addition of Mjalli does not cure the deficiencies of the above references because Mjalli is merely relied upon for teaching benzimidazole. Thus, none of the cited references teach or suggest the presently claimed liposome wherein the benzimidazole and lipid components are combined at the same time. Further, one of ordinary skill in the art would not have predicted that benzimidazole could be incorporated in a liposome with a PC:PS ratio of 1:1 based upon the methods disclosed in the cited references. This is demonstrated by Applicants' additional experiments in the Amendment filed June 27, 20072-, in which the benzimidazole compound is not incorporated into a

liposome wherein phosphatidylcholine and phosphatidylserine are in a ratio of 1:1, by using the method disclosed in the cited references, i.e., the benzimidazole compound was added after formation of the liposome. However, when the benzimidazole was added at the time of formation as presently claimed, the benzimidazole was incorporated into the claimed liposome, which would have been unpredictable based upon the disclosures of the cited references. Moreover, as evidenced by the experimental data in the Rule 132 Declaration submitted January 17, 2008, the presently claimed liposome provides unexpectedly superior incorporation of the claimed benzimidazole compound. The experimental results submitted in the Declaration of January 17, 2008, show that the amounts of the benzimidazole incorporated into the macrophages are the same between the example in which only the benzimidazole was added and the example in which a liposome of PC and PS in a ratio of 1:1 was added after the addition of the benzimidazole. These results indicate that the simultaneous addition of benzimidazole with PC and PS is crucial. Further, the experimental results in the Declaration show that when the benzimidazole is added together with PC and PS (1:1) upon formation of the liposome, the amount of the benzimidazole incorporated into the macrophages was unpredictably greater than those of Sample 1 and Sample 2."

These arguments are not persuasive. First of all, it should be pointed out that the primary reference (Aikawa, Kazuhiro) shows clearly that the claimed compounds are effective in treating hyperlipidemia and atherosclerosis even when added together with liposomes and not actually incorporating it into the liposomes. Surprisingly, the experiment conducted by applicant (the prior art inventor is the same as instant inventor), that is mixing the benzamidazole compound with liposomes, shows the activity which is the same as the controls where only benzimidazole is added. The same experiment was conducted was conducted at different times and yet, in the patent it shows the effectiveness and presumably when repeated by applicant, the same experiment shows no activity at all. This clearly shows that the experimental conditions in the patent were not the same as the conditions in the experiments reported in the

declaration. Secondly, since the liposomes came into existence in 1970s, the standard method of encapsulation of lipophilic active agents is to mix them along with the phospholipids in a lipophilic solvent, evaporating the solvent and hydrating the lipid film containing the lipophilic active agent. The process employed is the standard liposome making method. Therefore, though the claims are product by process claims, the lipophilic agent incorporation into the liposomes by mixing it with the phospholipid would be similar to any other lipophilic agent incorporation into the liposomes. The examiner also cites the reference of Radhakrishnan that shows the liposomal incorporation of hydrophobic steroids using the same standard method.

Applicant's arguments that Aikawa and Kitaguchi do not cure this deficiency because they are relied upon for merely disclosing a process of adding a compound as an active ingredient after liposomes have formed are not persuasive. Applicant is incorrect in this statement since these references show the same standard method of incorporation of lipophilic compounds by mixing with the phospholipid in an organic solvent, evaporation of the solvent and hydrating the phospholipid to form liposomes. Applicant's arguments that Schmidt is even less relevant because it is merely relied upon for disclosing liposomes to handle 'arteriosclerosis and extract cholesterol are not persuasive since one of ordinary skill in the art would be motivated to incorporate the benzimidazoles of EP into the liposomes with an expectation of obtaining at least an additive effect against this disease. Applicant's arguments that the addition of Mjalli does not cure the deficiencies of the above references because Mjalli is merely relied upon for teaching benzimidazole are not persuasive. Applicant is incorrect in this

statement since Mjalli is suggestive of the use of liposomes for these compounds though does not show the method of preparation. The encapsulation of lipophilic substances is already from the references of Aikawa and Kitaguchi. Applicant's arguments at the end of page 8 of the response relating to WO 97/35560 is not entirely clear to the examiner since this reference was not used in the rejection. 14C-labeled 2-methylbenzimidazole.The examiner has already addressed applicant's arguments regarding the unexpected results. With regard to higher amounts of incorporated benzimidazoles by instant method, the examiner once again points out that this is an art known method of incorporation of the lipophilic compounds within liposomes and the amounts incorporated are to be expected than the mere addition of active agent to the liposomes wherein the active agent attaches to the surface of liposomes.

3. Claims 1 and 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aikawa (5,387,600) of record in view of Aikawa (7,101,532) or Kitaguchi (7,008,614) or Schmidt (6,077,529), Mjalli (7,087,632) individually or in combination.

Aikawa (600) teaches that benzimidazole derivatives for the treatment of atherosclerosis (abstract and claims). What is lacking in Aikawa is the use of liposomes as the carriers.

Mjalli discloses liposomal formulations containing benzimidazoles for the treatment of atherosclerosis (abstract, col. 2, line 56, col. 37, lines 44-50 and claims). Mjalli however, does not specifically teach liposomes containing both phosphatidylcholine and PS. Mjalli

just teaches that liposomes can bye made from a variety of phospholipids on col. 37, lines 44-50).

Aikawa and Kitaguchi while disclosing liposomal compositions for radiography of a vascular disease (atherosclerosis) teach that liposomes are selectively taken up by vascular smooth muscle cells and macrophages. The liposomes contain PC and PS in 1:1 molar ratio (abstract, Examples 5, 68 and 9 of Aikawa; abstract, Examples 4, 5 and 8 of Kitaguchi).

Schmidt discloses that liposomes containing are useful in handling arteriosclerosis. The phospholipids, which could be used in making the liposomes, include PC and PS (abstract, col. 5, lines 24-34 and claim 4).

It would have been obvious to one of ordinary skill in the art to encapsulate or associate the benzimidazole derivatives of Aikawa (600) in liposomes since the references of Kitaguchi, and Aikawa each teach that the liposomes are selectively taken up by vascular smooth muscle cells and macrophages and since the reference of Schmidt teaches that liposomes can be used in handling atherosclerosis and Mjalli suggests the liposomal delivery of benzimidazoles for the treatment of atherosclerosis. .

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding Aikawa, Kitaguchi, Schmidt and Mjalli. Applicant's only argument is that Aikawa does not teach liposomes. This argument is not persuasive since the secondary references how to incorporate lipophilic active agents into the liposomes.

4. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK